**National Toxicology Program**
Toxicity Reports Series
Number 16

# NTP Technical Report on Toxicity Studies of

# Glyphosate

**(CAS No. 1071-83-6)**

## Administered in Dosed Feed to F344/N Rats and B6C3F$_1$ Mice

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**National Institutes of Health**

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The NTP report on the toxicity studies of glyphosate is based on disposition studies conducted at the College of Pharmacy, University of Arizona, Tucson, AZ, in November, 1987; 13-week studies performed between May and September, 1988, at Southern Research Institute, Birmingham, AL; and 14-day studies performed in 1990 at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

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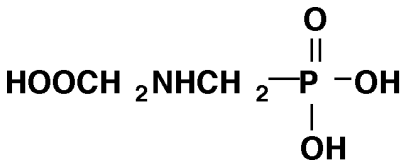
# Glyphosate



**Molecular Formula:** $C_3H_8NO_5P$

**CAS Number:** 1071-83-6

**Molecular Weight:** 169.1

**Synonyms:** Glyphosate, technical grade; Glycine, N-(phosphonomethyl); N-phosphonomethyl glycine; N-(phosphonomethyl)glycine; MON 0573; MON 2139.

## ABSTRACT

Glyphosate is a systemic, broad-spectrum, post-emergence herbicide used for non-selective weed control. It was selected for study because of its widespread use, potential for human exposure, and the lack of published reports concerning comprehensive toxicity or carcinogenicity evaluations.

Chemical disposition, 13-week toxicity, and mutagenicity studies of glyphosate were conducted. In disposition studies, male F344/N rats were administered an oral dose (5.6 or 56 mg/kg) of $^{14}$C-glyphosate. Blood, urine, fecal, and tissue samples were collected and analyzed for radioactivity. Within 72 hours after glyphosate dosing, 20-30% of the administered radioactivity was eliminated via urine, 70-80% via feces, and about 1% of the radioactivity remained in the tissues. Studies following oral, intravenous, and intraperitoneal administration of glyphosate indicated that the urinary radioactivity represented the amount of glyphosate absorbed and that the fecal radioactivity represented the amount unabsorbed from the gastrointestinal tract.

In the 13-week toxicity studies, groups of 10 male and female F344/N rats and B6C3F$_1$ mice were administered glyphosate in feed at 0, 3125, 6250, 12500, 25000, or 50000 ppm. Glyphosate administration induced increases in serum bile acids, alkaline phosphatase, and alanine aminotransferase activities in rats, suggesting mild toxicity to the hepatobiliary system. Clinical pathology measurements were not performed with mice. No histopathologic lesions were observed in the livers of rats or mice. There was no evidence of adverse effects on the reproductive system of rats or mice. Cytoplasmic alteration was observed in the parotid and submandibular salivary glands of rats and parotid salivary glands in mice. The salivary gland

effects of glyphosate were demonstrated to be mediated through an adrenergic mechanism which could be blocked by the adrenergic antagonist, propanolol.

Glyphosate was not mutagenic in *Salmonella*, and did not induce micronuclei in mice. The no-observed-adverse-effect level (NOAEL) for the salivary gland lesions was 3125 ppm in the diet for mice. A NOAEL could not be determined from the rat study.

# PEER REVIEW

## Peer Review Panel

The members of the Peer Review Panel who evaluated the draft report on the toxicity studies on glyphosate on July 10, 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members act to determine that the design and conditions of the NTP studies were appropriate and to ensure that the toxicity study report presents the experimental results and conclusions fully and clearly.

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## Summary of Peer Review Comments

On July 9 and 10, 1991, the Technical Reports Review Subcommittee of the Board of Scientific Counselors for the National Toxicology Program met in Research Triangle Park, NC, to review the draft technical report on toxicity studies of glyphosate.

Dr. Po Chan, NIEHS, introduced the short-term toxicity studies of glyphosate by reviewing the uses and rationale for the study, findings from chemical disposition studies, experimental design, and results.

Dr. Garman, a principal reviewer, said that the report was thoroughly prepared and detailed, and that it did an excellent job reviewing the background for the study and the available literature on glyphosate. He added that the isoproterenol/propranolol study included in the report is quite interesting and helps establish the mechanism for salivary gland alteration.

Dr. Garman said that certain details of the salivary gland alteration study should be clarified, namely, which type of glandular acinus within the submandibular salivary gland was most affected by glyphosate, and whether, in Table 11, only the parotid salivary gland was assayed in measuring the severity of changes brought on by glyphosate treatment. Dr. J. Mahler, NIEHS, said the severity grades were based on the parotid glands only.

Dr. Goodman, another principal reviewer, said the report was well-written. He suggested that the the lack of of any reproductive toxicity attributable to glyphosate treatment was an important finding and should be included in the abstract of the report.

After further discussion of editorial matters, Dr. Longnecker accepted the report on behalf of the panel.